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OBSERVATIONS ON THE RELATION OF ALLERGY TO IMMUNITY[1]

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The problem of the relation of allergy to immunity is one of fundamental importance to the theory of bacterial infection. The astonishing phenomenon of Koch and the diagnostic use of the tuberculin reaction have long attracted the attention of the world to the prominent rôle played by hypersensitiveness in tuberculosis, but it is only recently that widespread interest has been awakened to the fact that in many other forms of disease allergy exerts so important an influence upon the character of the symptoms and lesions, that to fail to reckon with it may mean to content oneself with an incomplete and inadequate understanding of the pathogenesis of the condition under consideration. We are still far from appreciating properly the influence of allergy in most infections—so far, indeed, that as a rule, except in the discussion of tuberculosis, one finds either no mention at all of allergy, or only the briefest reference to its existence, in even the best of modern clinical and pathological treatises dealing with bacterial diseases; and in the rare instances in which allergy is mentioned, clichés familiar in the literature on hypersensitiveness in tuberculosis are usually transferred, uncritically and without sound reasons, to other entirely different types of bacterial infection.

In the current journals, on the other hand, allergy is at present threatening to become one of the temporary fashions which periodically beset medical literature. At one time it has been the constitutional diathesis, at another time hydrogen-ion concentration, vagotonia and sympathicotonia, dietary deficiency, the vegetative nervous system, the endocrine glands, or the reticulo-endothelial system, on the basis of which swarms of writers have glibly explained the phenomena observed in almost every sort of disease. So it is becoming now with

[1] Presented before the Saranac Lake Medical Society, February 5, 1930.

allergy. One can already read in the recent literature enthusiastic announcements that gastric ulcer, epilepsy, pyloric stenosis, mucous colitis, pyorrhoea, high blood pressure, and many other conditions are the results of allergy, and that rheumatic pancarditis is merely an allergic reaction to the streptococcus viridans. These periodic fashions in medical thought, even though they do unfortunately provide a too easy vehicle for the publication of large numbers of uncritical ideas, and so increase enormously the difficulty and the burden of properly acquainting oneself with the literature on various subjects, nevertheless serve a useful purpose in focusing attention upon a particular phenomenon, and in finally provoking a critical examination of it until a proper balance of judgment is attained. It will be so with allergy. Out of the present awakening of interest in this subject we shall undoubtedly learn much about the nature and the effects of the hypersensitiveness acquired during the course of various forms of bacterial infection; and we shall at length even know accurately whether or not it is proper to say that allergy lies at the bottom of such conditions as gastric ulcer, nephritis, and rheumatic carditis.

Since the early studies of Koch, of Römer and of von Pirquet, allergy in tuberculosis has been regarded as intimately, if not inseparably, bound up with immunity—and certainly with fair justification from the standpoints of experimental observation and reasonable argument. If tubercle bacilli injected into normal tissues provoke only a sluggish local reaction, spread easily over the body and kill the animal with extensive visceral lesions, and if, when injected into immunized tissues, they call forth a rapid and intense local reaction but fail to infect the distant viscera, and, finally, if this rapid and violent reaction happens to be exactly the sort of reaction which is believed to be beneficial and protective in combating various bacteria and other injurious agents—namely, acute inflammation—it has seemed only the part of ordinary prudence to conclude that, in tuberculosis, the allergic body is protected by reason of its enhanced capacity for responding to the presence of the bacillus with acute inflammation. The idea is at once so plausible and so reasonable (and so comfortably teleological!) that I fear that to question its validity at all must seem to many who have become accustomed to it to be merely a time-consuming and a useless heresy.

I have said elsewhere (1), and I welcome the opportunity to repeat it here, that I am myself thoroughly aware of the theoretical virtues, and of the logic inherent in the view that allergic hypersensitiveness protects the body against bacterial infection. But I am not aware that the correctness of this view has been sufficiently well proven in the case of any one single infection to make one satisfied that the extensive destruction of tissue through allergy in tuberculosis is really essential for the maintenance of acquired immunity. It may be so; but it has not been proven to be so, and it is a matter of some importance that we know with certainty whether or not it is so. I shall have occasion in a moment to point out that in a different infection in which exactly the same interpretation of the importance of allergy in immunity has been unhesitatingly assumed to be correct, we have recently been able to show clearly that the assumption was entirely gratuitous.

I should like to emphasize that it is in no sense my purpose to try to prove as a general principle that allergy can be of no service to immunity. My interest lies rather in an impartial and critical enquiry into the precise nature and significance of allergy in different types of bacterial infection in some of which it may be that allergy plays an important rôle as a protective mechanism. As for tuberculosis, I may say that I was brought up on the belief in the necessity of allergy for the operation of immunity in this disease. During a number of years of study devoted to the pathogenesis of tuberculosis I used this belief as a matter of course and with relatively little questioning, in the attempt to interpret consistently the phenomena observed during the course of infection. However, numerous observations, apparently inconsistent with the theory, led me at length to examine more carefully the evidence upon which the theory rests. I have, in another place (1), pointed out that, at present, that evidence is quite too slender to warrant the conclusion that the tuberculous body cannot be immune unless it is allergic. Indeed, there were certain observations indicating, on the one hand, that a high degree of acquired immunity can exist independently of allergic hypersensitiveness, and, on the other hand, that a high degree of allergy may be present at a time when acquired immunity is greatly depressed. As a matter of fact, the only circumstances in favor of the identity of allergy and immunity were the facts that allergy and immunity in tuberculosis are ordinarily coexist-

ent, and that acute inflammation is to be regarded as a protective mechanism. I have for some months been engaged in the examination of these two aspects of the problem. Since allergy appears at some time during the course of most, if not all, bacterial infections, it is clearly desirable to study its relation to acquired immunity in different types of infection, with the idea that a comparative study of this nature might bring to light facts which would either establish definitely the necessity of allergy for the operation of immunity as a general principle in bacterial infections, or else would show that allergy and immunity are quite independent, dissociable, and unrelated phenomena in all infections, or finally that, although dissociable phenomena, allergic inflammation might in certain bacterial infections greatly assist the independent mechanism of immunity, while in others allergic damage to tissue might outweigh any good effects of the attendant inflammation. It has, furthermore, seemed advisable to examine experimentally certain of the claims made for acute inflammation as being, in itself, an efficient mechanism of immunity—claims upon which so much of the faith in the virtue of allergy is based.

If one turns to the literature on the relation of allergy to immunity, there will be found a surprising variety of dogmatic statements which usually rest upon no better foundation than the determination of the writer to believe that in the allergic reaction he must be witnessing always an operation of immunity. For example, one of the most prominent French authorities on tuberculosis writes that the latent tuberculous focus "always contains living, virulent bacilli walled about by fibrous tissue . . . . which, because of the existence of allergy, resists the destructive action of the poisons of the bacilli and hinders the extension of the lesion. When allergy becomes depressed this resistance disappears, the focus becomes softened" and extension takes place (3). Now this, like so many other statements about the virtue of allergy, is a mere assertion. There is no observation on record which indicates that the enhanced susceptibility of allergic tissues to tuberculoprotein can prevent the destruction of connective tissue. On the contrary, it is quite certain that allergy is frequently the direct cause of the necrosis of the connective tissue which encapsulates a lesion teeming with tubercle bacilli and saturated with tuberculoprotein.

Again, it is commonly stated, though it has certainly never been proved, that "allergy represents an enhanced capacity of the tissues to react protectively against the invading microörganism;" or, when an investigator is confronted with observations which indicate that immunity may persist after allergy has been lost, it is usually stated rather cryptically that "allergy is a stage in the development of immunity." Still other writers will declare in even less informing phrases that "allergy is an index of immunity," that "allergy is a function of immunity," that "allergy is a phase of immunity" and so on. The common idea running through all of these various expressions is that in some way allergy *must* be linked up with immunity.[2]

One of the few clearly defined expressions of opinion about the relation of allergy to immunity is the well known theory of Krause who has attempted to found his belief in the value of allergy on definitely understandable principles. His concept of the situation, which has found widespread acceptance, has been termed a "mechanical theory" of immunity, for it rests on the belief that allergy acts as a "mechanical barrier" which retards the spread of infection. Krause believes that "the outstanding and significant feature of tuberculo-immunity in guinea-pigs is not so much the complete inhibition of the activities of tubercle bacilli as a retardation of their spreading within the body," and that it is "the allergic exudative or inflammatory reaction . . . . that serves to impede the further passage of bacilli" (5). Similarly,

[2] It is rather unfortunate that the word "immune" is applied so indiscriminately to all sorts of states which occur after the body has been exposed to foreign protein parenterally—states which often have nothing whatever to do with the establishment of resistance to primary harmful effects of the proteins or bacteria introduced. A great amount of confusion and misinterpretation in the literature can, I believe, be traced directly to the term "immune reaction," which may be used by one writer to mean simply a state of altered reactivity of the body toward a particular bacterial product, with no implication that the changed state of reactivity brings about a heightened resistance to infection, but which will be understood by a second writer as connoting a state of resistance. Since every detectable change which occurs in the body fluids and cells after the introduction of bacteria is spoken of on all sides as an "immune reaction," it becomes less difficult to understand why so many of these changes which have never been shown to be advantageous in protecting the body against infection are nevertheless widely regarded as protective—as immunity reactions in the true sense.

Opie (7) in his Harvey Lecture last year, expressing his belief that allergic inflammation retards the spread of bacteria, stated that "in human tuberculosis inhibition of dissemination is one of the most conspicuous features of the disease in adults who have sustained the usual infection of childhood. In contrast with the tuberculosis of infancy and early childhood, pulmonary tuberculosis of adult type fails to implicate the nearest lymph nodes even when it is scattered over a whole lung" and "miliary tuberculosis is rarely if ever seen."

I, myself, have never seen a case of progressive adult pulmonary tuberculosis in which the lymph nodes at the hilum were not implicated. It is quite true that the involvement of the nodes is not nearly so extensive as it is in the primary infection, but histological examination invariably shows the presence of tubercles, usually with caseation. The striking thing seems to me to be not that bacilli fail to reach the nodes, but that they cannot proliferate as freely there as they do in the non-immune child during the primary infection. If the same number of bacilli which reach the regional lymph nodes in adult phthisis found their way into the nodes of a non-immune child, the most extensive lesions would undoubtedly result. As for the relative rarity of miliary tuberculosis in the adult, this is not the result of the failure of bacilli to reach the blood stream, for it is well known that bacilli have been repeatedly cultured from the blood during progressive pulmonary infections in adults in whom miliary tuberculosis failed to occur despite the blood-stream infection. One should not conclude from the lack of permanent lesions in an organ in the immune body that no bacilli were carried by the blood to that organ. The fact that the viscera are not riddled with tubercles in cases of adult phthisis is a result rather of the fact that, in the body with acquired immunity, the disseminated bacilli cannot proliferate freely where they lodge, but tend to die out. It is quite true that the rate at which bacilli spread from a local site of infection appears to be slower in the immune body than in the normal one, but I am unable to agree that retardation of spread is in any sense as important a factor in immunity in tuberculosis as is inhibition of the growth activity of the bacilli. I may recall that the immediate spreading of bacilli throughout all the tissues of an immune animal by the intravascular injection of a fine suspension of organisms will not produce miliary tuberculosis, and will be followed

by far less extensive permanent lesions in the internal viscera than will occur when the same number of bacilli are deposited even locally in the skin of a non-immune animal, from which site their spread to the viscera will be delayed for a number of days. Regardless of any question of the rapidity with which the bacilli were spread throughout the body, therefore, it is clear that in the immune animal something prevented the free growth of the bacilli where they lodged in the viscera, and that in the non-immune animal the absence of this 'something' permitted the bacilli to proliferate freely and progressively. Granted that an allergic reaction met each bacillus where it lodged in the immune body, if the outstanding and significant feature of immunity were actually a retardation of the spread of that bacillus rather than an inhibition of its proliferation, a progressive, destructive lesion would develop in the viscera at each site of lodgment of the injected bacilli, as happens in the non-immune body, instead of the contrasting regression of lesions with death and disintegration of many of the bacilli which is so familiar in the immune body under these conditions. It seems scarcely necessary to dwell further on the fact that one of the most important things which happens in immunity in tuberculosis—I believe unquestionably the most important thing—is that the bacilli, through some as yet undetermined mechanism, are prevented from living and proliferating as freely in the immune body as they do in the normal one. The chief problem in the matter of immunity in tuberculosis appears to me to lie, therefore, in the question—how is this inhibition of growth of the bacillus effected?

For many, this question appears to be satisfactorily answered by the assumption that, since acute inflammation effectively destroys and inhibits the growth of various bacteria, the inflammatory allergic reaction effects the destruction of the tubercle bacillus. Since any antibacterial virtue of acute inflammation lies in the fact that the reaction involves the escape of fluid and phagocytic cells from the blood into the tissues, it is fundamentally necessary, in the consideration of any particular infection, to enquire how well the fluid and cells of an inflammatory exudate are able to inhibit the activities of the infecting organism. In tuberculosis, as is well known, the search for specific lysins, whether within the phagocytes or in the plasma of the immune body, has been completely unsuccessful. There is no question that

the proliferation of tubercle bacilli is restrained, and that they tend to die out in the lesion of reinfection in the immune body, but there is much question whether these effects are the effects of lysins. Certainly neither lysins nor bactericidal properties have ever been satisfactorily demonstrated in the plasma of the immune body or in the fluids at the site of a tuberculous allergic reaction. That increased speed of phagocytosis occurs in reinfection is rather generally agreed upon, but it is far from clear that the phagocytes effect an active, specific lysis of the ingested bacilli. We know, in fact, that the tubercle bacillus lives surprisingly well within many of the phagocytes brought to the spot by inflammation—so well, indeed, that certain recent investigators have even expressed the opinion that if the production of the phagocytic monocytes of the body and their tendency to ingest tubercle bacilli could be checked, the body would be protected, for the reason that the bacilli would no longer have any favorable place in which to live (6). I do not pretend to subscribe to this view, for it is clear, I think, that tubercle bacilli can proliferate extracellularly in the body; but I cite it in order to bring out the point that, in considering questions of immunity, it is never enough to rest content with the mere fact of phagocytosis without enquiring whether or no the phagocytes are able to destroy efficiently the microörganisms which they take up. In reading most discussions of the relation of inflammation to immunity, one derives the impression that the writers believe implicitly that phagocytes have the power of digesting everything which they ingest. Having gotten the microörganism within a phagocyte, they rest content in the assumption that the microörganism will be promptly and surely destroyed. In tuberculosis, there is certainly no proof that I know that phagocytised bacilli are more likely to die than bacilli remaining outside of phagocytes in the immune body. *In vitro*, Mrs. Lewis and I have repeatedly seen tubercle bacilli proliferate to actual colony formation within living phagocytes taken from immune animals, and this can be observed to occur within the animal body as well. Similarly, one never thinks of the pathology of leprosy without the memory of mononuclear phagocytes laden with living lepra bacilli, and other instances of the survival of microörganisms within phagocytic cells come readily enough to mind. On the other hand, it is quite clear that tubercle bacilli may

fail to grow, and ultimately disappear in great numbers *outside* of phagocytes in the immune body, as any study of the fate of bacilli in caseous areas where there are no living cells will easily show. This can be followed very clearly in many situations, but it is perhaps most readily observed in a study of the fate of bacilli in disseminated tubercles. When bacilli are numerous in the phagocytic epithelioid cells of a tubercle, necrosis of the centre may be expected to occur, for the bacilli are usually concentrated in the central, original part of the tubercle, and it is a very common occurrence that the phagocytized bacilli, instead of being destroyed and digested by the phagocytes, proliferate within these cells and ultimately destroy them. At the time when necrosis is in progress, *i.e.*, when one finds the nuclei of the phagocytic epithelioid cells pyknotic and undergoing fragmentation, bacilli can be found in numbers in the dying area. Somewhat later, when all cell outlines have been lost and the necrotic, coagulated area stains uniformly pink with eosin, bacilli are still frequently present in considerable numbers, and may be clearly seen to be multiplying there. However, as the nuclear fragments gradually disappear, and the caseous area perhaps begins to be partly or completely hyalinized, the bacilli lying extracellularly in the dead area frequently become fewer and fewer in number and may disappear completely. The actual extracellular disintegration and fragmentation of the bacilli in such areas is not difficult to observe, and it becomes evident from a careful study of such lesions first, that tubercle bacilli can multiply within the phagocytic cells of the tubercle; second, that the destruction of the phagocytes rather than of the ingested bacilli is a very common result of phagocytosis; third, that the bacilli may proliferate, also, outside of the phagocytic cells; and finally, that cessation of growth and disintegration of bacilli outside of the phagocytic cells is very common indeed in the body with acquired resistance. That bacilli may also grow poorly and disintegrate *within* the mononuclear phagocytic cells of the blood and tissues of the immune body there is no doubt whatever, as a study of regressing disseminated tubercles in the immune body will show, and as Mrs. Lewis and I have frequently observed *in vitro*; but certainly there is no evidence that the interior of a phagocyte is a less favorable soil for their growth than are extracellular, uninflamed, positions in the body with acquired resistance. I call

attention to these facts because I think that the question: "Just what, if anything, does allergic inflammation bring to an infected site which is necessary for the inhibition of growth of tubercle bacilli?" is not only a fair question to place before those who assure us that allergic inflammation is necessary for immunity, but is a question the answer to which may go far toward the clarification of our knowledge of immunity in tuberculosis.

Obviously, if allergic hypersensitiveness implied merely a tendency to the prompt outpouring of an inflammatory exudate, one might be less concerned about the matter from a practical standpoint, for the allergic inflammation could be fairly enough regarded as possibly beneficial, and certainly not seriously harmful in most cases. But unfortunately, hypersensitiveness means *primarily* that allergic tissues are far more readily damaged and killed by tuberculoprotein than are the tissues of the normal body. The inflammation of allergy is merely an evidence of the fact that the innocent tuberculoprotein acts as a violent, necrotizing poison in the hypersensitive body. In the light of this fact, which is continually before the pathologist in the form of the widespread allergic necrosis encountered routinely at autopsy, one can hardly be content to speak complacently, and theoretically, about the necessary and beneficial effects of allergic inflammation, while slurring over the fact that, as far as is known at present, most of the death of tissue which occurs in the tuberculous body is directly a result of allergic hypersensitiveness. Since allergy, in tuberculosis, ordinarily results in extensive death of tissue as well as in inflammation, it becomes imperative, it seems to me, to enquire carefully into the precise value of allergic inflammation, and to determine whether or not acquired immunity is able to act efficiently in the absence of hypersensitiveness in this disease.

I should like to mention some experiments which form a part of an attempt which we have been making to analyze the effect of allergic inflammation upon the progress of various infections. As I have said above, the two familiar bases of the belief that allergy is necessary for immunity are, first, the fact that acute inflammation is ordinarily protective, and second, the fact that allergy and immunity are usually coexistent. Regarding the first of these points, while it is undoubtedly true that acute inflammation is, fundamentally, a protective mecha-

nism, it certainly does not follow, either through logic or from observation, that an enhanced capacity for reacting with inflammation is always necessary for the protection of the immune body, in which other efficient methods of defense are developed. We may recall that the naturally immune body may respond to the invasion of bacteria with much less inflammation than the susceptible body, and yet protection is complete. Regardless of this, however, it has seemed important to examine a little more closely the effect of uncomplicated acute inflammation upon bacteria. Those who believe that immunity is achieved especially through the prompt throwing out of an inflammatory exudate about invading bacteria, usually state as an argument in favor of their belief that it has been shown that an inflamed area is resistant to bacteria implanted in it. Now it has, indeed, been known for a long time that the growth and spread of *certain* bacteria are inhibited if those bacteria are implanted into tissues or serous cavities which are inflamed at the time when the bacteria are introduced. I think, however, that it is unwise to generalize too sweepingly about the matter from what is known at present, for only a limited variety of bacteria have been used in such experiments, and it is hardly to be expected that all pathogenic microörganisms, with their different bodily composition, and their different rates of growth within the animal body, will be affected in the same manner by the same circumstances. As a matter of fact, although Opie (8) and others have shown that if streptococci are deposited in an acutely inflamed serous cavity the animal will be protected against infection, Clark (9), on the other hand, has shown that no protection is demonstrable if pneumococci are used in such experiments. Clark's experiments are of particular interest in that they demonstrate that as few as ten pneumococci will regularly cause a rapidly fatal infection in rabbits, even when deposited in an inflamed serous cavity containing an abundant and fresh polymorphonuclear exudate.

Similarly, Cobbett and Melsome (17) found that, although an area of prepared acute inflammation constitutes a site of local resistance to the streptococcus erysipelatis or bacillus pyocyaneus injected into it, no protection could be demonstrated when anthrax bacilli, diphtheria bacilli or pneumococci were injected into inflamed areas.

As still another instance which should put us on our guard against

too hasty generalizations, I may mention the fact that although granulating wounds have long been well known to be very resistant to infection with certain pyogenic bacteria, such wounds have recently been shown to be extraordinarily susceptible to infection with the spirochaete of syphilis (10).

Indeed, regardless of any demonstrated resistance of inflamed tissues to streptococci, staphylococci, or colon bacilli, it should be remembered that, as far as tuberculosis is concerned, in the only experiments on record in which tubercle bacilli were implanted into prepared areas of acute allergic inflammation, infection was found to be favored rather than retarded (11).

It is clear from these considerations that it is of prime importance to study the effect of inflammation upon the particular organism which one has under consideration, rather than to generalize about that organism from experiments in which other bacteria were used. But aside from this point, I think that when we are dealing with the question of the bearing of allergic inflammation upon immunity there are also certain time relationships which have to be considered somewhat more carefully than they have been. It must be remembered that much of the confidence of those who regard allergic inflammation as an essential mechanism in immunity springs from the results of the numerous investigators who have shown that the activities of certain bacteria are inhibited when those bacteria are deposited in sites of *previously prepared* inflammation. In such experiments an irritant is first injected, let us say, into the peritoneal cavity. After inflammation is established, the bacteria are introduced; and it is then noted that the bacteria spread less rapidly, and that the animal survives the infection longer, or even recovers completely, as compared with the rapidly fatal outcome in controls in which the bacteria are injected into the normal peritoneal cavity. Now, without question, such experiments show clearly that an inflamed peritoneum is more resistant to the particular bacteria employed than is the normal peritoneum; and it is on the basis of this, and other similar experiments, that numerous writers make the leap to the conclusion that *therefore* the inflammation of allergy prevents the spread, and inhibits the activities, of the bacteria which induce an allergic reaction in the hypersensitive body. I say "make the leap to the conclusion" for the reason that,

aside from the fact that the particular bacterium under discussion may never have been tested in this manner, it is one thing to implant bacteria into a prepared inflammatory exudate, and quite another thing to implant them into the uninflamed tissues of the immune body, as is the case in reinfection. In the latter instance a period of time must elapse between the deposition of the bacteria in the tissues and the appearance of an effective amount of inflammation about them. In the allergic body this period of time is much shorter than it is in the non-allergic body, but it is rather important to determine whether or not it is long enough, nevertheless, to permit the bacteria to gain a foothold or to spread, before a sufficient amount of inflammation appears. In other words, it seems to me necessary to try to reproduce the sequence of events which happen during an allergic response to bacteria, namely, deposition of the bacteria in the tissues, followed by the prompt and progressive development of inflammation about them, rather than to create an entirely anomalous and reversed situation by first setting up an inflammation and later injecting bacteria into the inflamed area.

Dr. Bull, Miss McKee and I have recently carried out a variety of experiments of this nature (4). Our purpose was, primarily, to try to dissociate the effect of allergic inflammation from any other factors which may serve to protect the body with acquired immunity, in order that we might be able to form an estimate of the protective power of an uncomplicated, accelerated acute inflammation in the face of various bacteria. In the particular experiments about which I shall speak, we used the rabbit as the experimental animal, and the bacillus of fowl cholera as the infecting organism. This microörganism was chosen for the reasons that the rabbit is highly susceptible to infection with the bacillus, that the infection runs a rapid and fatal course, and that a high degree of acquired immunity can be produced by the injection of dead cultures.

We first set about to determine the minimal lethal dose of this bacillus for the rabbit, and we found that, in the normal rabbit, as few as three bacilli would produce infection, with death within 36 hours. It is indeed probable that infection with a single bacillus under favorable conditions can kill a rabbit. We found, on the other hand, that immunized animals are able to survive the inoculation of one hundred

million times the number of bacilli which kills normal animals. Is acquired immunity to this organism chiefly a result of a more prompt allergic, acute inflammation occurring at the site of reinfection in the immune body? In order to test the efficacy of acute inflammation, alone, in combating the bacillus we carried out a series of experiments on non-immune animals. Instead of using chemical irritants to produce the inflammatory reaction, we felt that it would be more to the point to study the effect of an allergic inflammation. We therefore made use of the fact that rabbits which have been immunized to pneumococci respond to the intracutaneous injection of soluble, bacteria-free pneumococcus antigen with brilliant allergic reactions. In our experiments we first produced such allergic reactions in rabbits which were hypersensitive and immune to pneumococci, but not to the bacillus of fowl cholera; and several hours later when the allergic inflammation was well established, we injected an average of four fowl cholera bacilli into the inflamed areas, and the same number of bacilli into the skin of normal control animals. I shall not enter into the details of the protocols further than to say that all except an occasional one of the test animals survived the injection of the bacilli into the areas of inflammation, whereas the control animals promptly died from the infection.

It is quite clear from these experiments that an area of established allergic inflammation is able to inhibit the activities of a small number of fowl cholera bacilli. This is in keeping with the experiments which I have mentioned, in which it has been shown by other investigators that the activities of certain other pyogenic bacteria are inhibited if the organisms are injected into inflamed areas. But, as I have said, this type of experiment does not really reproduce the events which take place in natural infection. Before we can draw conclusions about the protective value of allergic inflammation, we must know whether the body will be protected if the bacilli are injected *at the same time* as the allergic antigen so that, as happens in natural reinfection, the allergic reaction does not begin to develop until the bacteria have reached the tissues. We therefore injected the usual average dose of four fowl cholera bacilli *together* with the soluble pneumococcus antigen into pneumococcus immune rabbits and into normal, non-allergic controls. The allergic inflammation developed as usual in the animals

which were hypersensitive to the pneumococcus antigen, but, to our surprise, not only did this promptly developing inflammation fail to check the growth of the fowl cholera bacilli, but it actually tended to cause their earlier dissemination from the site, and the more rapid death of the animals in which the inflammation occurred, the test animals dying about twelve hours earlier than the controls. Since we had shown that the same form of inflammation, when fully established, is decidedly unfavorable to the activities of this bacillus, it must be clear that even when an established allergic inflammation is able to inhibit a particular microörganism, it does not necessarily follow that the immunity observed on reinfection results from the acute inflammation which appears shortly after the bacteria have reached the tissues. The period of time which elapses between the lodgment of the bacteria and the development of the allergic inflammation may be sufficient to permit the bacteria to gain a foothold in the tissues if they are not restrained by some other mechanism of acquired immunity; and local tissue conditions during the onset and development of inflammation may actually favor the growth and spread of the bacteria, as was clearly the case in the present experiments.

I should like to emphasize that in these experiments we introduced only a minimal number of bacteria (an average of four bacilli) into the tissues, and yet the activity of these few bacilli could not be checked by the promptly developing allergic inflammation—not even when the bacilli were injected together with amounts of antigen which set up a much greater allergic inflammation about them than those few bacilli themselves could possibly have called forth in animals allergic and immune to the fowl cholera bacillus. It is impressive that while immunized rabbits can survive the injection of more than three hundred million fowl cholera bacilli, three bacilli are rapidly fatal to nonimmune rabbits, even when injected under conditions which provide for the development of a prompt and abundant acute inflammation about them. It is also of importance to point out that although an area of established inflammation inhibited the activity of the minute dose of four bacilli injected into it, such areas of established inflammation were powerless to prevent fatal infection when larger numbers of bacilli were introduced,—numbers which the animal with acquired

immunity could easily take care of with much less inflammation. I cannot enter here into further details of these experiments, but I may remark that we have followed minutely the fate of the injected bacteria, and the local effects of our inoculations upon the tissues, by microscopic study of several hundred sections of the lesions at different stages; and to dispel any doubt that the phagocytes which were called out by the effects of the soluble pneumococcus antigen were able to attack the fowl cholera bacilli, I may say that our sections show clearly that they phagocytized these bacilli and other test bacteria as well, although, of course, by no means as avidly as bacteria for which the animals had developed opsonins.

Now it is interesting and important to call attention to the fact that an examination of the protocols in the papers of previous investigators who are commonly cited as having shown that an area of inflammation produced by non-specific irritants has the power to protect the body against the invasion of certain bacteria, actually shows that the spread of the bacteria was retarded only when the inflammatory irritant was introduced some time (in certain instances 24 hours) *before* the bacteria were injected (8); (13); (14); (17); (25). Although such experiments have been widely used as evidence that allergic inflammation can prevent the spread of bacteria and protect the body, the protocols make it clear that no protection was observed when the bacteria and the irritant were introduced together. For example, in a very recent paper describing the effect of introducing streptococci into areas inflamed by aleuronat, Opie, pleading the cause of allergic inflammation, writes: "The experiments that have been cited show that the intensified inflammatory reaction of a sensitized animal will tend to prevent dissemination of bacteria from the site of infection" (8). The protocols in this paper, however, show that in the only experiment in which the inflammatory irritant was introduced at the same time as the bacteria, the rate of dissemination was not retarded, and no protection whatever was afforded the animal.

Again, in a recent review (18), it is stated along the same lines that "Cobbett and Melsome's work indicates that a non-specific inflammation such as that produced by mustard oil will prevent successful inoculation" of the streptococcus erysipelatis. It is, however, not stated that Cobbett and Melsome found that inflamed areas offered no pro-

tection against diphtheria bacilli, anthrax bacilli, or pneumococci; nor is it mentioned that the protocols in the paper of these investigators show that, although an area of established inflammation did inhibit the activities of streptococci deposited in it, if the streptococci and the inflammatory irritant were introduced at the same time, the resulting infection was actually more severe than it was in the control animals (17).

Indeed, in our own experiments, as I have said, there was a definite acceleration of the death of the animals when the allergic antigen was injected at the same time as the bacteria. It is hardly necessary to point out that these results do not support the "mechanical theory" of immunity referred to above, which assumes that allergic inflammation appears rapidly enough on reinfection to prevent the immediate spread of bacteria by hemming them in. In the case of tubercle bacilli, it has been shown by Willis (21) that bacilli deposited locally in the skin of the normal body have already spread from the site at the end of an hour, and Kagayama (19) has shown that they actually reach the regional lymph nodes within five minutes after having been deposited in the peritoneal cavity. It is rather difficult to believe, therefore, that the allergic inflammation, which takes much longer to develop in tuberculosis, can prevent the immediate escape of bacilli from the site at which they lodge. On the contrary, as I have pointed out, it has been shown by Krause and Willis (11) that the deposition of tubercle bacilli into areas of prepared inflammation actually favors their spread and leads to more extensive infection. If immediate local fixation of bacteria really occurs in the body with acquired immunity (and it apparently does occur), I believe that it is effected by a specific, precipitin-like process, rather than by the allergic inflammation which appears some time after the bacteria have reached the tissues.[3]

[3]Since this was written I have carried out experiments which demonstrate clearly that the local fixation of the pneumococcus in the immune body is effected primarily by an immediate, specific, agglutinative process which appears to involve, also, a process of adsorption of the bacteria to the tissues. The bacteria are specifically agglutinated and 'precipitated' on to the tissues, and are held fixed where they lodge before any inflammation has appeared, in contrast to their immediate spread from the site in the non-immune animal; and this process of fixation is quite as effective in the absence of allergic inflammation as it is in its presence (Proceedings of the Nat'l. Acad. of Sc., July, 1930).

The experiments on the fowl cholera bacillus which I have just described were designed only for the purpose of testing the effects of inflammation in itself, dissociated from any other protective mechanisms which may be active in the immune, allergic body. It is, of course, to be expected, that in various infections immune antibodies may confer upon the allergic inflammatory exudate specific protective powers which the fluid and phagocytes of exudates in the non-immune body do not possess. It is, however, necessary to demonstrate this circumstance in each particular instance rather than merely to postulate it. It is of interest in this connection that Opie has shown that purulent exudates may be very poor in opsonins (20), and that Clark (9) found that not only did an acute purulent inflammation fail to protect the body against pneumococci deposited at the site, but that no protection was afforded by the exudate even when the pneumococci were first exposed to the antibodies of immune serum before being introduced into the area. Our experiments on the fowl cholera bacillus are presented as constituting only an approach to the problems involved in allergic inflammation, but they may at least serve to warn us against forming hasty conclusions based upon the general proposition that inflammation is, in itself, a protective mechanism, without regard for the specific conditions under which the inflammation develops.

The precise value of allergic inflammation must certainly be more carefully investigated. Further experiments bearing upon the matter are in progress in our laboratory, but they are too incomplete to be discussed profitably at the present time. I should like, however, to mention briefly some observations which have a bearing upon the second argument commonly advanced by those who believe allergy to be necessary for immunity, namely, the argument that allergy and immunity are always coexistent.

I have, in another place (1), called attention to the fact that there are observations on record in connection with tuberculosis which, to my mind, disturb seriously the acceptance of the common statement that hypersensitiveness and immunity parallel each other in this disease. However, it seemed important to study the matter in other infections, with the idea that perhaps in some of them these two phenomena might be more easily dissociated than in the case of tuberculosis. It was felt

that syphilis should be one of the first infections to be studied from this standpoint, for the reason that this disease resembles tuberculosis in numerous ways. To mention some of the points of resemblance between these two infections I may remind you that both the spirochaete and the tubercle bacillus call out especially the mononuclear, rather than the polymorphonuclear, wandering cells; that the lesions produced by the spirochaete may be histologically indistinguishable from those produced by the tubercle bacillus; that caseation of the lesions occurs in both infections; that a high degree of acquired immunity appears in syphilis as in tuberculosis, but that in neither infection has it been possible to demonstrate specific bactericidal or growth-inhibiting antibodies; that allergy appears during the course of both diseases; that both commonly run a protracted course; and that certain other clinical and pathological similarities have been striking enough to cause various investigators (Ranke for instance) to draw a close parallel between the manner of evolution of these two diseases. I wish, further, to call attention to the fact that, as in the case of tuberculosis, acquired immunity in syphilis, also, has been flatly assumed to be the result of allergy. Krause, discussing his belief in allergy as a mechanism of immunity, writes that on reinfection in tuberculosis the reaction "is comparable to what we observe when we . . . . reinoculate an animal that has a chancre with a fresh dose of syphilitic virus. The reaction is accelerated and abortive and partakes more of the nature of a pure inflammation" (15). Ramel (12), also contending that immunity is a result of the allergic inflammation, writes that since the tertiary stage of syphilis is the stage in which allergy is most apparent, "treatment with salvarsan . . . . prevents the development of the tertiary stage, and the patients are, therefore, cured before they have reached the stage of allergy. It is to this," he continues "that one must attribute the increasing number of reinfections noted during recent years." In other words, treatment before the stage of allergy means treatment before the development of immunity. Finally, in a recent textbook on allergy and immunity (16) it is stated directly that the "relative immunity (in syphilis) is really a hypersensitiveness. . . . . Persons with syphilis are protected from reinfection by the local hypersensitive reaction which occurs at the seat of reinoculation." The experiments which I am about to report will show that there is really no basis for these and other similar assumptions.

Now it was indeed shown by Noguchi some years ago that syphilitic rabbits may react allergically when an emulsion of spirochaetes is injected intracutaneously (22). Noguchi called this the "luetin" reaction, and it has since been demonstrated that syphilitic human beings also react allergically to emulsions of spirochaetes at certain periods of the disease. The fact that spirochaetes, harbored in the body for months with relatively little effect upon the tissues, begin in the so-called tertiary stage to produce widespread caseous necrosis is sufficient, in itself, to suggest that an allergic state has been developed, and in fact it is especially in this tertiary stage that cutaneous allergy can be demonstrated by the injection of luetin. There are, however, many reasons for believing that immunity appears long before the tertiary stage. There are, also, reasons for believing that allergy is not actually present in the stage of the chancre as it has been assumed to be; and since no satisfactory investigation of the relation of allergy to immunity in syphilis had been carried out, Dr. Chesney, Dr. Turner and I (23) infected rabbits with strains of spirochaetes derived from human lesions, and at different periods after the inoculation, we injected measured doses of virulent spirochaetes intracutaneously into the syphilitic animals and into normal control animals, and studied the local effect carefully by gross inspection of the inoculated areas, and by microscopic examination of the areas removed at frequent intervals following the inoculation. Some of the test animals were reinfected while they were carrying the chancre of first infection; others at a period of months following the healing of their chancres. Briefly, at the site of inoculation in the control animals there always occurred the progressive development of an ulcerating chancre, usually reaching a size of several centimetres in diameter. In contrast to this, the sites of inoculation in the previously syphilitic rabbits showed at no time the slightest reaction of any sort, aside from the negligible, immediate reaction to the injection of the material containing the spirochaetes—a slight and transient hyperaemia which was in no sense greater in the syphilitic animals than in the controls. Several hundred sections of areas of reinfection removed at frequent intervals after the inoculations were studied microscopically in comparison with similar sections taken from the control series. It was found that in the control animals there appeared a slight and transient acute inflammation as a response to

the material injected, but after several days the characteristic mononuclear inflammatory reaction made its appearance and the lesions progressed steadily to chancre formation and ulceration. The areas of reinfection in the syphilitic animals, on the other hand, showed microscopically exactly the same degree of slight, transient acute inflammation, but following this the tissues returned to their normal state and remained so, or at most a few insignificant groups of mononuclear cells would appear after the lapse of several days. Not only was there no more prompt and marked allergic inflammation on reinfection, but the specific reaction in the reinfected animals was never at any time in any way comparable in intensity with that observed regularly in the controls.

The objection might be raised that the rabbit's skin is not a very favorable site for the study of allergic reactions, and the objection is undoubtedly valid in the case of tuberculosis. It is, however, by no means valid in the case of allergy in numerous other infections. The cutaneous allergic reactions to the pneumococcus, for example, are brilliant in the rabbit, and it was in fact in the skin of the rabbit that Noguchi worked out the luetin reaction for syphilis. However, in order to rule out any such objection, we have made inoculations into the cornea and testis as well. These sites in the syphilitic animal were as completely indifferent to reinfection as was the skin.

In brief, there was not the slightest suggestion of an accelerated, intensified allergic reaction in the tissues of the reinfected animals, whether a chancre was present at the time of reinfection, or whether the syphilitic animals were past that stage of the infection. On the contrary, it was most strikingly clear that the tissue-cells of the syphilitic rabbits were immune to the spirochaete in the best sense of the term "immunity"—*i.e.*, they were completely indifferent to the presence of the virus. Regardless of any allergic reaction which the rabbit may exhibit to the spirochaete under different circumstances, in the period of infection represented by the rabbits in our experiments we can say with certainty that a remarkable state of cellular immunity was present in the complete absence of any detectable allergic reaction to the organisms of reinfection. Whether the allergic reactions described by Noguchi and others were dependent upon the injection of the highly concentrated antigen which was used by them, or whether their ani-

mals were simply in a different stage of the infection I cannot say. For the present argument it suffices to point out only that in spite of the fact that the reinfecting dose which we used was far larger than could ever be possible in natural infection, our syphilitic animals were immune without exhibiting the slightest allergic inflammatory response. I do not doubt that allergy occurs during the course of syphilitic infection. As I have said, the caseous tertiary lesions attest the presence of allergy, and many investigators have clearly demonstrated cutaneous hypersensitive reactions in this stage of the disease. The important thing learned from our experiments, however, is that in the rabbit, acquired immunity to reinfection in syphilis can exist independently of any allergic inflammation. There are excellent reasons, into which I cannot enter, for believing that the same is true of man. It is probable that in syphilis, as in tuberculosis, acquired immunity may not be able always to effect the death of all of the organisms which enter the body in reinfection. This point remains a matter for study. But as far as the body cells are concerned, the immunity observed in these experiments represents, to my mind, an ideal form of tissue immunity, *i.e.*, a state in which the infecting organisms apparently cannot proliferate as readily as they can in the non-immune body, but more important, in which the tissues themselves are not destroyed by the microörganisms or their products, whether directly or through hypersensitiveness. Such an immunity is obviously infinitely superior to the postulated "immunity achieved through allergy," in which it is supposed to be necessary that the tissues must be damaged and even killed locally for the protection of the body as a whole.

I think that these experiments on immunity in syphilis have an important bearing upon the question as to whether it is justifiable to assume the necessity of allergy for immunity as a general principle in infections. In not a single infection has allergy been proven to be necessary for the successful operation of acquired immunity. In the case of syphilis we have an instance of an infection in which hypersensitiveness is certainly not necessary for immunity. I would, personally, avoid generalizations at this stage of our knowledge, but if any generalization has to be made, it would seem wiser to proceed from what we know to be true in at least one infection rather than from

what is generally assumed to be true in all. It is obviously important to attempt to dissociate allergy and immunity in still other infections. Dr. Brown and I are at present making a study of infection with the pneumococcus, with the idea that passive immunization may yield information regarding the alleged necessity of allergy for immunity to this organism.[4] I may say that Ramel (12) quotes Yessner as having shown that in experimental sporotrichosis allergy develops, but rapidly disappears, and that the animal, after complete loss of allergy, enjoys a perfect acquired immunity.

Certainly, if it were clear that allergy is as non-essential for immunity in tuberculosis as our experiments have shown it to be in syphilis, the most serious efforts should be directed toward the development of more efficient methods of desensitization, for the purpose of preventing the tissue damage which results from allergic hypersensitiveness. In the case of tuberculosis, however, the exact relationship between allergy and immunity is not yet satisfactorily understood. There are, at least three obvious ways in which the rôle of allergy in immunity in tuberculosis might be investigated: first, one might study the effect of reinfection in animals with acquired immunity, but in which allergy has been abolished by desensitization; second, one might strive to induce acquired immunity without a concomitant development of allergy; and finally, one might strive to establish a state of allergy to tuberculoprotein by methods which would not simultaneously confer immunity. The first of these problems has been under investigation in our laboratory for some time by Dr. Rothschild and Mr. Bernstein. The method adopted consists in rendering guinea-pigs allergic and immune by the injection of the Rl bacillus of low virulence, and then desensitizing the animals by the injection of increasingly large doses of tuberculin. When desensitization is established, the animals receive a measured dose of virulent H37 bacilli in the anterior chamber of the eye, and the state of desensitization is maintained continually by daily injections of large amounts of tuberculin. The result of the virulent inoculation is controlled at autopsy by comparison with the results of injecting the same dose of virulent bacilli into the eyes of orig-

[4] Since this paper was written these experiments have been completed, and have shown clearly that allergic inflammation is not necessary for the operation of acquired immunity to the pneumococcus (26).

inally normal animals and of animals which were allergic and immune at the time of injection. There are numerous difficulties encountered in such experiments, one of the major matters of concern being the maintenance of thorough desensitization throughout the experiments without producing at any time a perifocal or constitutional tuberculin reaction. The infected eye can of course be inspected directly each day to control the question of perifocal inflammation, and careful temperature measurements and the general condition of the animal must serve to check the absence of constitutional reactions following the injections of tuberculin. Intercurrent infections have, unfortunately, reduced the survivors of several series of animals to a number in no way sufficiently large to serve yet as a basis for conclusions. The method, however, I believe to be an applicable one, and it promises to yield definite information in time. It is obvious that everything, in such experiments, depends upon accurate knowledge concerning the maintenance of densensitization during the entire period of the experiment, and every precaution is being taken to acquire this information in a satisfactory way.

Regarding the second of the methods outlined above as possible approaches to the problem before us, namely, the attempt to produce immunity without allergy, I have the permission of Dr. Arnold Branch, of Harvard, to quote from an unpublished manuscript which he sent to me, the highly interesting information that, following up experiments previously reported in collaboration with Petroff and Jennings, he has been able to produce acquired immunity in tuberculosis in the complete absence of allergy, by means of a special method of immunization with dead tubercle bacilli. He is engaged in further enlarging his experimental series, and his completed report will indeed be of great interest, for the matter is obviously one of crucial importance.

I have wished, in this paper, to draw attention to some of the various facts which argue against the wisdom of the popular attitude of resignation in the face of the destructive effects of allergic hypersensitiveness in tuberculosis. There was a long period in the history of pathology during which every response of the body to injury was regarded as harmful and undesirable. The remarkable *Aufklärung* of the last seventy-five years revealed the potential virtues of so many of these

reactions that, for a time, the pendulum swung almost to the other extreme, and many pathologists became unwilling to doubt the teleological virtue and necessity of any of these responses of the body, adopting, after a fashion, the view of the celebrated Dr. Pangloss, that all things must happen for the best in this best of all possible worlds. At present, however, we have attained a middle position, in which we believe that the various coördinated reactions of the body do exist, fundamentally, for some serviceable use, even though, as in the case of anaphylaxis, we may as yet be unable to define that use; but we also know that these reactions may, under certain conditions, be not only useless but actually harmful, and it has become clear that we can very profitably dispense with some of them when they occur under certain circumstances. This much we have learned even about hypersensitiveness. We have learned, for example, the wisdom of abolishing hypersensitiveness in asthma and in hay fever, and of prophylactic desensitization previous to the injection of protective sera. It is perhaps time for the reëxamination of the value of certain other types of reaction in relation to the different conditions under which they occur. Certainly I feel this to be urgent in the case of allergy in tuberculosis, for if it can be established that the tuberculous body can be spared the danger (one might, indeed, say "the certainty") of untoward allergic accidents, without interfering with the free play of immunity, the development of efficient methods of desensitization might prove to be of the utmost value in many cases of tuberculosis.

In conclusion, it is of considerable interest to recall here that nearly twenty years ago Dr. Baldwin wrote, in a discussion of allergy and immunity in tuberculosis:

> "It seems reasonable to attempt to lessen the high sensitiveness seen in many (tuberculous) patients and in the scrofulous children particularly. I cannot follow Wolff-Eisner in his belief that abolition of tuberculin skin and fever reaction leads to danger of further infection" (24).

Unfortunately perhaps, during the years which have followed this expression of opinion, the belief of Wolff-Eisner has become more and more firmly embedded in the minds of most students of tuberculosis without, it is fair to say, any important, crucial experimental or clinical facts having been adduced in support of it. In this paper I have

sought to point out that today, more than ever before, there are reasons for looking askance at facile statements about the necessity of allergy for immunity in tuberculosis, and to stress the need for a serious examination of the effects of freeing the tuberculous body, by desensitization, from the harmful results of hypersensitiveness. In passing, I have mentioned certain general lines of investigation, the further development of which may possibly assist in the clarification of this important problem.

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THE RELATION BETWEEN PHOSPHORUS, CHLORIDE AND BICARBONATE IN THE SERUM OF RACHITIC AND NORMAL RABBITS

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The following study was made on rabbits who had been made rachitic with the McCollum diet No. 3143. The rabbits were put on this diet at the age of three or four weeks and blood samples taken after they had been on the diet for 20 to 40 days. At that time, the X-ray of the bones showed in all cases rachitic changes, sometimes very marked, and the serum phosphorus had, generally, dropped far below the normal level. The serum calcium, as always in rickets, was, generally, found to be of normal magnitude, except in four cases, in which the phosphorus was normal and the calcium very low, that is, where the serum presented the picture found in tetany. In the following study these four cases are not included, but only the cases in which the blood findings were typical of rickets, that is, in which the calcium was normal and the phosphorus decreased.

The values for calcium, phosphorus, chloride and bicarbonate in the serum of these rabbits are tabulated in Table I. It was found that the animals with the lowest values for phosphorus had, as a rule, comparatively high values for *both* bicarbonate and chloride. If only cases with about the same bicarbonate values are compared, one finds the highest values for chloride in the most severe cases of rickets (severe, as judged by the decrease of phosphorus). If, on the other hand, cases with about the same chloride values are compared, the most severe cases have the highest values for bicarbonate. The relationship between phosphorus, chloride and bicarbonate is best expressed by plotting the values for phosphorus against the sum of chloride and bicarbonate, as has been done in Fig. 1.

TABLE I

Rachitic rabbits

(Values in millimols per 1000 cc. of serum)

NUMBER	HCO_3	Cl	P	Ca
96_1	31	105	0.87	3.35
90	21	117	0.86	3.50
95_1	25	107	0.68	3.23
142	26	100	1.27	3.20
150_2	23	107	0.98	3.53
145	19	107	1.36	3.38
154	18	105	1.41	3.45
168	24	99	1.18	3.63
164	25	111	0.67	3.45
162	26	108	1.15	3.25
167	27	105	0.66	3.22
94_2	27	108	0.68	3.05
96_2	33	107	0.68	3.35
97_1	17	122	1.13	3.12
47	22	107	1.23	2.75
57_1	27	113	0.37	3.18
56_1	26	118	0.35	3.50
7	19	105	1.32	3.57
6	27	108	0.77	3.58
8	30	103	0.87	3.47
12_1	33	100	1.03	3.65
16	20	111	0.94	3.28
17	30	104	0.87	3.48
20	31	102	1.03	3.53
22	29	106	0.97	3.40
23	19	111	1.17	2.50
24	26	105	0.86	
25	32	100	0.85	3.72
26	22	111	0.83	3.10
27	25	111	0.87	3.52
95_2	22	107	1.10	3.15
45	31	104	1.13	3.48
43	31	111	0.52	3.50
57_2	23	109	0.63	3.33
56_2	24	112	0.81	3.23
149	24	107	0.78	3.40
151	30	107	0.52	3.00
94_3	30	105	0.90	2.75
96_3	33	99	0.95	3.33
95_3	27	104	1.06	3.35
97_2	24	111	0.88	3.03
49_2	28	107	0.64	3.20
57_3	22	113	0.68	3.05
56_3	32	105	0.68	3.00
13	26	105	0.87	3.48
15	28	105	0.65	3.50
12_3	24	105	1.00	3.60
11	31	100	1.13	3.50

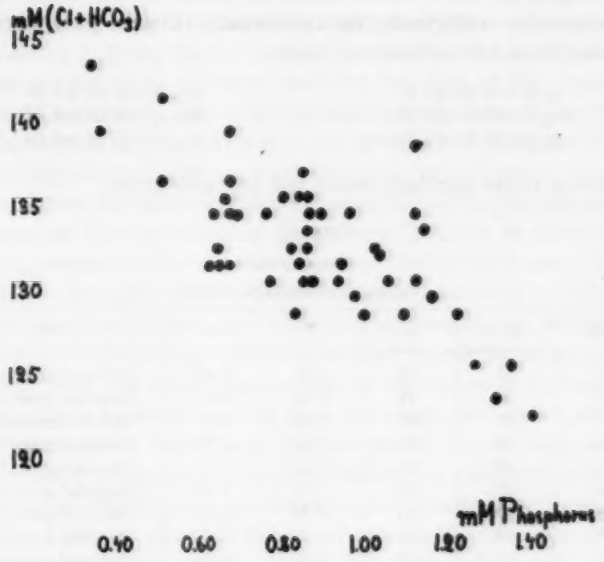

FIG. 1. THE RELATIONSHIP BETWEEN THE PHOSPHORUS AND THE SUM OF CHLORIDE AND BICARBONATE IN THE SERUM OF RACHITIC RABBITS

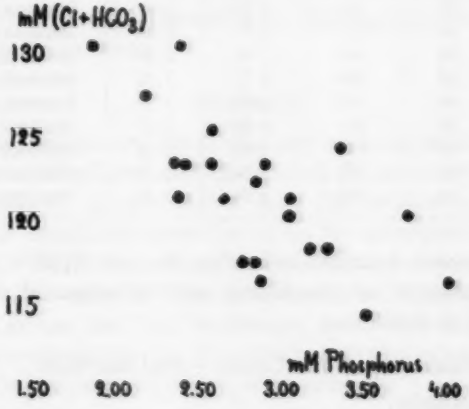

FIG. 2. THE RELATIONSHIP BETWEEN THE PHOSPHORUS AND THE SUM OF CHLORIDE AND BICARBONATE IN THE SERUM OF NORMAL RABBITS

This figure is based on the following statistical data: If r signifies the correlation coefficients, the correlations between phosphorus (1), chloride (2) and bicarbonate (3), are:

$r_{13} = -0.34 \pm 0.13$ $\quad$ $r_{12.3} = -0.68 \pm 0.08$
$r_{12} = -0.37 \pm 0.12$ $\quad$ $r_{13.2} = -0.69 \pm 0.08$
$r_{23} = -0.53 \pm 0.10$ $\quad$ $r_{23.1} = -0.75 \pm 0.06$

The errors are standard errors, not probable errors.

TABLE II

Normal rabbits

(Values in millimols per 1000 cc.)

NUMBER	HCO_3	Cl	P	Ca	DIET
88	33	98	2.37	3.30	Oats and green leaves
89	30	94	2.42	3.05	Oats and green leaves
87	28	100	2.18	3.25	Oats and green leaves
86	30	101	1.84	3.03	Oats and green leaves
115	20	98	2.83		Oats and green leaves
114	27	99	2.59	3.12	Oats and green leaves
121	20	95	3.52	2.63	Oats and green leaves
119_1	11	106	2.87	3.38	Oats and green leaves
119_2	22	100	3.06	2.68	Oats and green leaves
118_1	14	105	3.29	3.13	Oats and green leaves
118_2	21	96	4.03	2.70	Oats and green leaves
111	26	98	2.37	3.12	Oats and green leaves
282	20	104	2.90	2.88	Stenbock stock diet
280	25	99	2.58	2.97	Stenbock stock diet
279	15	103	2.77	2.80	Stenbock stock diet
278	26	96	2.38	2.59	Stenbock stock diet
277	22	99	3.77	2.02	Stenbock stock diet
285	26	95	3.04	2.78	Stenbock stock diet
286	20	103	2.84	3.17	Stenbock stock diet
288	19	103	2.66	3.31	Stenbock stock diet
289	21	98	3.18	2.85	Stenbock stock diet
290	25	100	3.36	3.15	Stenbock stock diet

The regression equation indicating the quantitative relationship between variations of phosphorus and variations of chloride and bicarbonate, is as follows:

(1) $\quad$ Phosphorus $= -0.038$ Chloride $- 0.043$ Bicarbonate

that is, practically,

(2) $\quad$ Phosphorus $= -0.04$ (Chloride $+$ Bicarbonate)

The equations express relationship between variations, not between total amounts. Fig. 1 is based on equation 2.

Equation 2 shows that if the sum of chloride and bicarbonate increases one millimol, the most probable variation of the phosphorus will be 0.04 millimol, that is, the variations of the sum of chloride and bicarbonate are 25 times as great as the variations of phosphorus. The relationship shown in Fig. 1 cannot, therefore, be interpreted as osmotic compensation, by which on the decrease of the serum phosphorus there has been an increase of other electrolytes, in order to maintain the osmotic pressure of the serum at a constant level; such a compensation would, at the most, show a 1:1 relationship between variations of chloride plus bicarbonate and variations of phosphorus, while Fig. 1 shows a 25:1 relationship. If the total fixed base in the serum remains constant, then one might assume that on the decrease of phosphorus there ought to be an increase of some other acid, but such a substitution of chloride or bicarbonate for phosphorus on the basis of their valency could not possibly show more than a 3:1 relationship between variations of chloride and bicarbonate and variations of phosphorus.

In Fig. 2 may be seen that in normal animals also the same relationship between phosphorus, chloride and bicarbonate is present. These animals were fed either on the Steenbock stock diet or on oats and green leaves. On this latter diet the animals show the enormous variations in concentration of serum bicarbonate described by Osborn, Nosum and Samsum (1), depending on whether they have taken more oats or more green leaves.

DISCUSSION

We are at present not able to offer any explanation of the relationship between phosphorus and the sum of chloride and bicarbonate, described above. It was shown that the relationship cannot be explained as osmotic compensation or as the substitution of one acid for another. There is, however, the possibility that parallel with the variations of phosphorus there have been variations of some other acid in the serum, and that the changes in chloride and bicarbonate represent a compensation for the variations of this other acid, not for the rather insignificant variations of phosphorus.

METHODS

Phosphorus, Fiske and Subbarow (2).

Calcium, Fiske and Logan (to be published).

Chloride, Fiske and Lin (see the paper by Fiske and Sokhey (3)).

Bicarbonate, carbon dioxide combining power according to Van Slyke and Harrington (4). This method gives, of course, only an approximate value for the bound bicarbonate, but the error is not great enough to influence our conclusions.

SUMMARY

Both in rachitic and normal rabbits the phosphorus in the serum varies in opposite direction to the sum of chloride and bicarbonate.

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FOETAL BLOOD STUDIES

I. The Oxygen Relationships of Umbilical Cord Blood at Birth

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It is our intention in the present series of studies to investigate those components of foetal blood which may be concerned in the onset of respiration. While such phenomena as the initiation of breathing, the apnea of intra-uterine life and the clinical syndrome of asphyxia neonatorum, have been explained by various hypotheses, these theories have never been supplemented by studies of the foetal blood,—a fact that seems particularly remarkable when one recalls the many and fruitful blood chemical investigations that have dealt with the regulation of respiration in the adult.

The dearth of such quantitative studies on the blood at birth is the more surprising when it is remembered that a large proportion of stillborn foetuses show at autopsy no pathological change, such deaths being usually described as due to "asphyxia" or "acute anaerosis." Thus, Peckham (1), in a statistical study of 1461 stillborn foetuses in this Clinic, finds that in 28 per cent the cause of death was not demonstrated; while in an additional 19 per cent it was listed simply as "asphyxia." In view of the chemical nature of respiratory control in adults, it appears altogether probable that a considerable number of these unexplained deaths result from chemical changes in the foetal blood incident to labor, but just what the alterations are, to what extent they proceed and beyond what limit foetal death must ensue, are as yet entirely unknown.

Most intimately associated with respiration, of course, are the oxygen relationships of blood. In adults the oxygen content of arterial and venous blood has received extensive study from Lundsgaard (2), who has investigated particularly the significance of the mean capil-

lary unsaturation of blood in various conditions. The oxygen unsaturation of a given sample of blood he defines as the difference between the oxygen-combining power (or capacity) and the actual oxygen content; in other words, this term expresses the amount of reduced or unoxygenated hemoglobin present in the blood. Now, if the arterial unsaturation is A and the venous unsaturation V, the value for the capillary unsaturation, C, must change from A to V during the passage of the blood through the capillaries, the mean value of C being $\frac{A+V}{2}$. The importance of this conception of oxygen unsaturation is readily appreciated when it is considered that it not only represents the condition of the blood actually available for tissue metabolism but also is the determining factor in the production of cyanosis. Thus, it has been shown by Lundsgaard that when the mean oxygen unsaturation of capillary blood, which normally ranges between 3 and 4 volumes per cent, reaches 6.5 volumes per cent, cyanosis results, the characteristic heliotrope color being produced by the high concentration of reduced hemoglobin.

As far as we have been able to discover, no complete data on the oxygen relationships of foetal blood at birth have been published. In 1928, however, Blair Bell (3) and his associates, in the course of certain studies on the nature of malignant neoplasms, reported a single mean figure of 9.02 volumes per cent for the oxygen content of the blood of the umbilical vein and of 5.85 volumes per cent for that of the umbilical artery at birth; studies on oxygen capacity were not included. More recently Haselhorst (4), while investigating the blood pressure in the umbilical vessels, determined the oxygen content of umbilical vein blood before and after the beginning of respiration, his figures for specimens taken at these two times being 8.77 and 12.91 volumes per cent, respectively. In another group of cases he made similar observations on the blood of the umbilical arteries and found that prior to respiration its oxygen content averaged 3.08 volumes per cent, while a few seconds after breathing had begun it reached 10.32 volumes per cent. Since neither of these investigations were concerned with the physiology of respiration, they naturally did not include determinations of the oxygen unsaturation of foetal blood; nor can this expression be calculated from their published data.

The present communication reports a complete study of the oxygen relationships of foetal blood in 16 cases. The majority of the mothers were multiparae who had rapid, spontaneous deliveries without anaesthesia and whose babies cried vigorously shortly after birth. While our interest has centered chiefly on the condition of the foetal blood immediately before the onset of respiration rather than its state *in utero*, we have for purposes of comparison included one case in which umbilical cord blood was obtained at Caesarean section just before the removal of the child. This we have taken as representing the oxygen relationships of umbilical blood as they exist *in utero*.

METHODS

Immediately after the birth of the child, before the delivery of the placenta and prior to the onset of respiration, two Kelly clamps were placed on the cord in close apposition to the vulva and a second pair a few inches from the baby, all four clamps being applied as nearly simultaneously as possible. By cutting between the clamps at the two ends of the cord, a segment of cord about 12 inches long was usually obtained, tightly clamped at either end, and containing in its vessels enough venous and arterial blood for a complete gas analysis.

The blood specimens which represent the oxygen relationships of foetal blood *in utero* were obtained as follows: At Caesarean section, performed after infiltration of the abdominal wall with novocaine, a small incision about 4 cm. in length was made in the uterus, the membranes ruptured and a loop of umbilical cord immediately withdrawn, This was then clamped and cut in the manner just described.

As soon as the cord was obtained, the blood samples from the umbilical artery and vein were drawn by means of a needle and syringe containing about 2 cc. of light paraffin oil, and then transferred to a 15 cc. centrifuge tube containing paraffin oil and a sufficient amount of sodium oxalate to prevent clotting. The maternal blood specimens were likewise taken under oil from the patient's arm vein, as nearly as possible at the moment of delivery. The oxygen content of the arterial blood of the mother was not determined but was estimated as 95 per cent of the oxygen capacity, as experience shows that error arising from such an approximation would be negligible for the purposes of this study (5). For each oxygen capacity determination, 3 cc. or

more of blood were aerated in a separatory funnel for 10 minutes, following which the sample was analyzed for its oxygen content.

All analyses were done with a calibrated, constant volume Van Slyke apparatus in accordance with the method of Van Slyke and Neill (6).

RESULTS

The detailed results of the study are listed in Tables I and II, while the average values for the different determinations are shown diagrammatically in Chart I. Viewing the findings as a whole it is evident that the oxygen relationships of the foetal and maternal bloods differ widely.

Particularly striking is the contrast between the oxygen capacities of the two bloods, that of the foetus averaging 20.8 volumes per cent and that of the mother 15.4 volumes per cent. This, it may be noted, is not a new finding, but is in keeping with the work of Williamson (7) and others (8, 9) on the blood of the new-born, and that of Bland, Goldstein and First (10) and others (11, 12) on the "physiological anemia of pregnancy." Recalling that an oxygen capacity of 18.5 volumes per cent is equivalent to 100 per cent of hemoglobin on the Haldane scale, our figures indicate that the hemoglobin content of the blood of the foetus averages 112 per cent as compared with only 84 per cent for the mother. Using the same method of analysis, the blood of ten normal non-pregnant women showed an average oxygen capacity of 18.9 volumes per cent, equivalent to a hemoglobin percentage of 102. In the foetus on the other hand, it is not uncommon to meet hemoglobin percentages of 120 per cent, and in our series the lowest concentration of hemoglobin in foetal blood was 101.5 per cent.

The arterial blood of the foetus, reaching it through the umbilical vein, is low in oxygen as compared with that of the mother. At birth, indeed, its arterial blood contains on an average even less oxygen than the blood of the maternal arm vein. *In utero* the oxygen content of the umbilical vein appears to be about 3 volumes per cent higher than at birth, a condition that might be expected, since at birth the placental circulation is impaired by the retracting uterus. The low oxygen content of the umbilical vein blood becomes more striking if, instead of referring to the quantity of oxygen present in volumes per cent (cc. of

gas per 100 cc. of blood), we express it as a percentage of the total amount of oxygen with which the blood will combine; or, in other words, in terms of percentage saturation. It will be seen then that

TABLE I

Showing the oxygen relationships of maternal and foetal blood at birth expressed in volumes per cent

CASE NUMBER	MATERNAL				FOETAL			
	Cap.	Cont. Art.	Cont. Ven.	Cap. Unsat.	Cap.	Cont. Art.	Cont. Ven.	Cap. Unsat.
1	14.5	13.8	10.0	2.6	20.2	9.8	2.4	14.1
2	13.8	13.1	10.1	2.2	22.4	12.3	5.9	13.3
3	17.1	16.2	12.8	2.6	18.8	9.5	1.4	13.3
4	14.8	14.1	9.9	2.8	20.5	10.2	3.3	13.8
5	15.6	14.8	10.2	3.1	22.5	12.7	6.0	13.1
6	16.3	15.5	11.0	2.9	21.0	8.2	1.3	16.3
7	17.0	16.2	12.8	2.5	20.9	8.8	2.7	15.1
8	16.0	15.2	12.9	2.0	19.5	11.2	5.3	11.2
9	15.2	14.4	10.5	2.8	19.8	9.9	2.3	13.7
10	12.4	11.8	9.0	2.0	22.3	12.2	5.4	13.5
11	15.4	14.6	10.0	3.1	20.8	9.3	1.5	15.4
12	15.5	14.7	10.5	2.9	22.5	13.2	5.7	13.0
13	16.1	15.3	11.0	3.0	19.9	10.4	2.0	13.7
14	14.9	14.2	10.6	2.5	20.3	10.1	2.9	13.8
15	16.6	15.8	13.3	2.0	20.8	9.8	1.9	14.9
Average...	15.4	14.7	11.0	2.6	20.8	10.5	3.3	13.9

TABLE II

Showing oxygen relationships of maternal and foetal blood in utero expressed in volumes per cent

CASE NUMBER	MATERNAL				FOETAL			
	Cap.	Cont. Art.	Cont. Ven.	Cap. Unsat.	Cap.	Cont. Art.	Cont. Ven.	Cap. Unsat.
1	15.6	14.9	10.8	2.8	20.9	13.3	6.3	11.1

while the arterial blood of the mother is usually 95 per cent saturated with oxygen and the maternal venous blood 71 per cent saturated, the arterial blood going to the foetus *in utero* is only 63 per cent saturated, and falls at birth to approximately 50 per cent.

The venous blood of the umbilical arteries at birth is often nearly depleted of oxygen, the figures in our series ranging from 1.3 to 6.0 volumes per cent, with an average of only 3.3 volumes per cent. *In utero* the content of the umbilical arteries showed a similar low figure, 6.3 volumes per cent. If now the difference between the oxygen content of the umbilical vein and artery is calculated, it will be seen that a relatively large quantity of oxygen is lost by the umbilical vein blood during its passage through the foetus. It should be noted, however, that this difference in oxygen content may not be taken as an index of

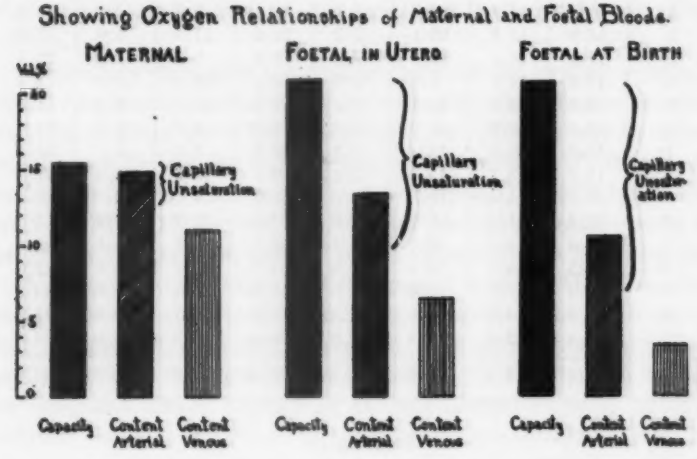

CHART I

foetal oxygen consumption on the same basis as we would measure oxygen consumption in the adult, since a certain portion of this foetal blood, owing to the anatomical "shunts" of the foetal circulation, passes through the capillaries several times and accordingly becomes more greatly reduced.

The greatest difference between the oxygen relationships of maternal and of foetal blood, however, is met in the mean capillary unsaturation, which in foetal blood is several times that found in the blood of the mother. In the present series the figures for the capillary unsaturation of maternal blood are slightly lower than Lundsgaard's average

range for adults, which he stated to be 3 to 4 volumes per cent, but even if his upper figure for normal be taken, it will be seen that at birth the mean capillary unsaturation of foetal blood is three times, and *in utero*, more than twice that of adult blood.

DISCUSSION

It now becomes profitable to inquire into some of the mechanisms responsible for these differences between foetal and maternal blood. Of primary importance in this connection is the oxygen tension, or the partial pressure of oxygen, to which the foetal blood is exposed as it passes through the villous capillaries. While obviously the actual tension of oxygen in such locations cannot be measured directly, it may be estimated on sound physico-chemical principles by reference to the oxygen dissociation curve of hemoglobin. Thus, when blood is exposed to the oxygen tension present in the pulmonary alveoli, or 100 mm. of mercury, it reaches nearly complete saturation with oxygen. Moreover, the oxygen tension to which the blood is exposed may be decreased at first very substantially without affecting materially the percentage saturation of the blood with oxygen: at 50 mm. tension, for instance, the blood is still 85 per cent saturated. As the oxygen tension is further decreased, however, the amount of oxygen with which hemoglobin will combine decreases so rapidly that blood exposed to a tension of 30 mm. will show only about 65 per cent saturation. Reasoning conversely, we may say then that normal blood showing 65 per cent saturation with oxygen has been subjected to an oxygen tension of about 30 mm. of mercury. Recalling now that the blood of the umbilical vein *in utero* is only 63 per cent saturated with oxygen, it becomes manifest that this blood in its passage through the villous capillaries must have been exposed to a very low tension of oxygen. It is true that the carbon-dioxide tension and the electrolyte content of blood modify somewhat the amount of oxygen with which it will combine, but making allowances for maximum variations in these constituents, it seems unlikely that umbilical vein blood is exposed to an oxygen tension of more than 40 mm. of mercury,—or less than half the tension to which adult blood is subjected in its passage through the pulmonary capillaries.

In view of the low oxygen tension to which umbilical blood is exposed, the high hemoglobin content of this blood assumes particular significance, since there is general agreement that the usual response of adult blood to low oxygen tensions is a rapid increase in the number of erythrocytes and in the amount of hemoglobin. Thus, in individuals living at high altitudes, high figures for hemoglobin are constantly found, Fitzgerald (13) stating that among acclimated individuals there is a rise of 10 per cent in hemoglobin for every 100 mm. drop in barometric pressure. The increase in hemoglobin, moreover, seems to be associated with an increased hematopoietic activity of the bone marrow, and during the expedition of Barcroft (14) to the Peruvian Andes, a marked increase in the number of reticulocytes was noted, which number fell to normal after the descent. Barcroft and other students of the subject believe that the purpose of the increase in hemoglobin is to provide a larger storehouse of oxygen in the blood from which the necessary tension may be maintained in the plasma. Similarly, it seems altogether probable that the high hemoglobin content of foetal blood is essentially an adaptive or "acclimatization" mechanism resulting from constant exposure to low oxygen tensions. Plausibility is lent to such a view by the fact that as soon as the foetus is born and is subjected to atmospheric conditions, the high hemoglobin and increased number of erythrocytes fall rapidly, so rapidly, indeed, that icterus neonatorum often results. Further support to this belief is found in the observation that foetal blood at birth shows evidence of increased bone marrow activity with nucleated red cells, polychromatophilia, anisocytosis and poikilocytosis, changes which disappear in the first few weeks of extra-uterine life (15).

Turning finally to the actual oxygen supply to the foetal tissues, it should be noted that our principal findings, namely, the low oxygen content of the foetal blood and its high oxygen unsaturation, will be still further accentuated if we consider the various anatomical "shunts" of the foetal circulation. Thus, the blood supplying the lower extremities of the foetus will be seen to contain the same low oxygen content as that of the umbilical arteries, while the blood supplying the brain will contain less oxygen than the umbilical vein blood due to its admixture with blood returning from the lower extremities. The degree of oxygen unsaturation of the capillary blood will be cor-

respondingly increased and, in view of Lundsgaard's findings that a mean capillary unsaturation of 6.5 volumes per cent or more is always associated with cyanosis, it becomes apparent that the full term foetus *in utero* must exist in a state of considerable cyanosis. It must not be inferred from these findings, however, that the foetus *in utero* normally suffers from oxygen want, since the amount of oxygen lost by the umbilical vein blood in its passage through the foetus, would seem to be plentiful for an organism resting in a dormant state in a medium at constant body temperature. Further confirmatory evidence that the foetus *in utero* does not normally experience oxygen want is supplied by the lactic acid content of foetal blood, a subject which will be discussed in a future report.

CONCLUSIONS

1. The oxygen relationships of foetal blood, both *in utero* and at birth, differ widely from those of maternal blood.

2. The principal characteristics of foetal blood in its relation to oxygen are the high capacity, the low arterial content, the very low venous content, and, as a result of these three factors, an extremely high capillary unsaturation.

3. The greatest difference between foetal and maternal blood in relation to oxygen is found in the mean capillary unsaturation which in foetal blood at birth is three times, and *in utero* more than twice that of adult blood.

4. The very high unsaturation of foetal blood in respect to oxygen indicates that the full term foetus *in utero* exists normally in a state of cyanosis.

5. The evidence suggests that the high oxygen capacity, or hemoglobin content, of foetal blood is an adaptive or "acclimatization" phenomenon due to the low oxygen tension to which the foetal blood in the villous capillaries is subjected, a tension that is estimated as being less than 40 mm. of mercury.

6. Viewed by adult standards the blood reaching the foetal tissues is low in oxygen, but for the needs of the foetal organism it is evidently adequate.

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BOOK REVIEWS

The Newer Knowledge of Bacteriology and Immunology. By Eighty-Two Contributors. Edited by Edwin O. Jordan and I. S. Falk. 1196 pp. $10.00. (*The University of Chicago Press, Chicago, 1928.*)

This book is a compilation of eighty-three chapters, by almost as many authors, on many of the most recent developments in bacteriology and immunology. To review these chapters even briefly would require the writing of a small volume. In general, the authors have not only given the results of recent research in the subjects covered but have also given brief and, in most cases, sufficient reviews of previous work. In only a few instances are the theories of the author allowed to overshadow critical and unbiased reviews of the subjects discussed. Such subjects as The Newer Knowledge of the Morphology of Bacteria, The Dissociative Aspects of Bacterial Behavior, Bacterial Associations, Bacterial Oxidations and Reductions, The Action of Ultraviolet Light on Bacteria, The Bacteriophage, Filterability of Microörganisms, A Theory of Microbic Virulence, and The Mechanism of Agglutination, serve to illustrate the fact that there is a "Newer Bacteriology" and to indicate the rapid progress of one of the most recent branches of biology. Such subjects as The Nature, Distribution, and Functions of Soil Microörganisms, The Root Nodule Bacteria of Leguminous Plants, The Rôle of Bacteria in the Treatment of Sewage, Some Problems in Water Bacteriology, Bacteria in Milk, Contamination and Deterioration of Food, The Spirochaetes, Filterable Viruses, Bacteria in Relation to Plant Diseases, Communicable Diseases of Laboratory Animals, Bacteria of the Intestinal Tract, Bacteria of the Respiratory Tract, and the chapters on Immunology, illustrate the wide scope of modern bacteriological research.

One is forced to recognize that bacteriology, starting a few decades ago as a branch of pathology, of the fermentative and other chemical industries, of agriculture and of sanitary science, has at a bound passed beyond the confines of a single department and, like chemistry, permeates almost every branch of medical and industrial science. It is the servant of them all and the inspiration of much of of the research that is being done. To the pathologist bacteria are agents producing certain types of injury; to the chemist, agents of chemical activity; to the clinician, surgeon and sanitarian, infectious or etiological agents; to the agriculturist, agents of soil fertility or plant disease; to the canning industry, agents of spoilage; to the dairy industry, agents of spoilage, animal disease or for the manufacture of desirable products; and to the immunologist they are antigens. In all these fields bacteria are studied for what they do rather than for what they are and pure bacteriology is incidental to applied bacteriology. That problems in pure bacteriology are crowding for investigation is attested by many of the

chapters in this book. About twenty-five of them are concerned with research which properly belongs to departments of pure bacteriology, departments which might properly occupy positions in university curricula similar to those of theoretical chemistry. It appears that bacteriology is destined to make its greatest advance along fundamental lines in the near future and that the solution of many practical problems awaits this advance.

It is hoped that in years to come this book will be followed by others of similar nature.

J. H. B.

Ueber das Problem der Bösartigen Geschwülste. By PROF. DR. LOTHAR HEIDENHAIN. 153 s. (*Julius Springer, Berlin, 1928.*)

In a stately volume with many plates, excellently printed from good photographs, Professor Lothar Heidenhain of Worms presents the results of his experimental studies in which he has injected autolysates of human tumors into mice.

Professor Lothar Heidenhain, the brother of Professor Martin Heidenhain, the anatomist in Tübingen, is the son of Rudolf Heidenhain and Fanny Volkmann, sister of the great surgeon, and was born in Breslau in 1860. He was assistant to Küster in Berlin and afterward professor of surgery in Greifswald.

It was his idea that although the cells of a tumor originating in man could not be successfully transplanted into a mouse, if the cells could be dissolved or deprived of their specificity there might remain an infective agent capable of producing a tumor in the mouse. This idea had occurred before to Keyser who attempted to destroy the specificity of tumor cells so that they might be transplanted, and met with some success.

Briefly, Heidenhain grinds up the human tumor tissue in Ringer's solution and covers it with toluol, after which it is kept for ten days or more in the incubator at 37°C. until all cells have disappeared. Freezing and warming were used with less success, and a fresh emulsion was also used. Such material, sometimes in extreme dilution was injected in various places in mice. In 1601 mice 94 tumors were produced, while Bashford reckons spontaneous tumors in mice at 1 to 2500.

But the type of tumor produced in the mouse had no relation to that of the human tumor. A carcinoma of the breast might produce a sarcoma in one mouse and a carcinoma in another. A human osteosarcoma generally produced mammary carcinoma, but sometimes sarcomas or nondescript tumors. One tumor only resulted from such injections, except in two or three cases in which two quite different tumors were found in different parts of the body. The site of the tumor bore no relation to the point of injection of the autolysate.

Most important of all, the tumor did not develop for a long time—in most cases after more than a year and in many after about two years. As an average, he says, one must wait about a year for the result of the injection.

When a tumor arising in such a mouse was subjected to the same prolonged autolysis and then injected into other mice, tumors were produced, sometimes after a long wait, but they bore no relation in type to that from which the autolysate was made.

The author argues that it is impossible that these should be spontaneous tumors. It is true that his inoculations of rabbits were quite unsuccessful, but they live longer than mice and the results are still to be awaited. He refers his results to Prof. Hanser and Prof. M. B. Schmidt, who were evidently very polite.

One has the impression that this very distinguished old worker has toiled very hard and is full of his idea, and a little impatient with pathologists who are so critical. It is very remarkable that he has found in his inoculated animals so many tumors, but then they are extremely old too. After one waits 25 months for the result of an injection in a mouse, the animal's allotted span is past, and if it presents a tumor then, there seems rather slight reason to suppose that it had any connection with that long forgotten inoculation. If such a thing is to be proven, it would seem that there must be some constancy in the results. The idea that the type of tumor depends on where the "agent" happens to lodge is not convincing and the effect should be more quickly recognizable. And it seems probable that if the statistics of spontaneous tumors were made from only such aged mice as these, the proportion might be much higher than Bashford's figures show.

Whether we can believe that in malignant tumors, of whatever animal, there is an agent which will withstand complete destruction of the tissue by prolonged autolysis, and when introduced in massive doses into the tissues of another animal will, after months, cause the formation of a tumor of some other kind, depending upon the type of tissue in which the agent has lodged, may be left to the reader to decide.

W. G. M.

Epidemic Encephalitis. Etiology, Epidemiology, Treatment. Report of a Survey by the Matheson Commission. 849 pp. (*Columbia University Press, New York, 1929.*)

Through the generosity of Mr William J. Matheson a committee undertook to review the work done on this important disease and to publish the available information on the etiology, epidemiology and treatment of encephalitis. The personnel of the committee is William Darrach, Chairman, H. S. Howe, Secretary, Haven Emerson, F. P. Gay, William H. Park, Charles R. Stockard, Frederick Tilney and Willis D. Wood. The survey was made by Dr. Josephine B. Neal, than whom no one better could have been chosen as she is doubtless the best informed physician in America, if not the world, on the subject of infections of the brain and its membranes. She was assisted by Helen Harrington, epidemiologist. The work of the Commission will not stop with this report, but subsequent ones will be made on causation, treatment and results.

The book is a small one, commendably so, and about half of the some 800 pages are taken up with a splendid bibliography prepared by Jean N. Baker, covering the period 1916–1928. The size of the bibliography, most of which belongs to a period of ten years, gives some idea of the importance which the disease has attained in the mind of the profession.

Perhaps the only adverse criticism of the report is that it starts with one published by certain Rumanian observers in 1916. The report states, "The indeterminate character of epidemic encephalitis renders conclusions concerning the nature of these previous epidemics uncertain." Diseases must start sometime. Poliomyelitis, as far as we know, dates from the next to the last decade of the eighteenth century and whooping cough from the third quarter of the sixteenth. Encephalitis, certain authorities to the contrary notwithstanding, certainly is an old disease, even if it was not recognized as an epidemic one, and nearly a century elapsed before poliomyelitis was regarded as an epidemic disease.

For purposes of modern research, however, the disease may be said to date as the Commission has it. The Survey shows its mastery in having condensed so much information into so few pages and future workers will be spared much useless labor by using it.

The chapter on Etiology describes the work done on cultivable bacteria, protozoa and the various groups of filterable viruses including the herpes virus and allied strains. Fortunately the Survey takes up other types of encephalitis, among them the post-vaccinal form.

As to treatment, the Survey is of great value, especially in pointing out the measures which have been found useless. The most interesting therapeutic measure is the use of Levaditi's rabbit-brain vaccine. "If Levaditi's strain 'C' is the etiologic agent of epidemic encephalitis this treatment rests upon a scientific basis. Many of the comments are favorable, but the data are as yet insufficient to enable us to reach definite conclusions."

The chapter on Epidemiology, while condensed, contains too much information to be considered in this review. It is an invaluable study covering all phases of the disease. This report is not only valuable in itself as a source of accurate information on the subject under investigation; it is a model for future workers in all lines. The enormous output of literature threatens to take on Frankensteinian proportions and as the German proverb has it, "We cannot see the wood for the trees." If reports as concise and accurate as this one could be issued say at ten-year intervals the problem of the hypertrophied, and alas! edematous, medical literature might be solved.

J. R.

BOOKS RECEIVED

The Female Sex Hormone. By Robert T. Frank, A.M, M.D, F.A.C.S. Part I. Biology, Pharmacology and Chemistry. Part II. Clinical Investigation Based on the Female Sex Hormone Blood Test. With 86 illustrations and 36 graphs. 1929. 8°. 321 pages. Charles C. Thomas, Springfield. $5.50.

Clinical Medicine for Nurses. By Paul H. Ringer, A.B., M.D. Illustrated. Third revised edition. 1929. 12°. 330 pages. F. A. Davis Company, Philadelphia. $3.00.

The Nutrition of Healthy and Sick Infants and Children. For Physicians and Students. By E. Nobel, C. Pirquet, and R. Wagner. Second revised edition

with 78 illustrations (including charts) and 6 tables. Authorized Translation by Benjamin M. Gasul, B.S., M.D. 1929. 8°. 243 pages. F. A. Davis Company, Philadelphia.

Surgical Diseases of the Thyroid Gland. By E. M. Eberts, M.D. With the Assistance of R. R. Fitzgerald, M.D. and Philip G. Silver, M.D. Illustrated with 48 engravings. 1929. 12°. 238 pages. Lea and Febiger, Philadelphia. $3.50.

Practical Local Anesthesia. And Its Surgical Technic. By Robert Emmett Farr, M.D., F.A.C.S. Second edition, thoroughly revised. Illustrated with 268 engravings and 16 plates. 1929. 8°. 611 pages. Lea and Febiger, Philadelphia. $9.00.

Diseases of the Chest and the Principles of Physical Diagnosis. By George William Norris, A.B., M.D., and Henry R. M. Landis, A.B., M.D., Sc.D. With a Chapter on the Transmission of Sounds Through the Chest by Charles M. Montgomery, M.D. and a Chapter on the Electrocardiography in Heart Disease by Edward B. Krumbhaar, Ph.D., M.D. Fourth edition, revised. 1929. 8°. 954 pages. W. B. Saunders Company, Philadelphia. $10.00.

Text-Book of Embryology. By Frederick Randolph Bailey, A.M., M.D., and Adam Marion Miller, A.M. Fifth revised edition. With 526 illustrations. 1929. 8°. 687 pages. William Wood and Company, New York, $7.00.

Modern Methods of Treatment. By Logan Clendening, M.D. With Chapters on Special Subjects. By H. C. Andersson, M.D.; J. B. Cowher, M.D.; H. P. Kuhn, M.D.; Carl O. Rickter, M.G.; F. C. Neff, M.D.; E. H. Skinner, M.D.; and E. R. DeWeese, M.D. Third edition. 1929. 8°. 815 pages. C. V. Mosby Company, St. Louis. $10.00.

The Blood Picture and its Clinical Significance. (Including Tropical Diseases) A Guidebook on the Microscopy of Blood. By Prof. Dr. Victor Schilling. Translated and edited by R. B. H. Gradwohl, M.D. Seventh and eighth revised edition with 44 illustrations and 4 color plates. 1929. 8°. 408 pages. C. V. Mosby Company, St. Louis. $10.00.

Practical Massage and Corrective Exercises with Applied Anatomy. By Hartvig Nissen. Fifth edition, revised and enlarged. By Harry Nissen. Illustrated with 72 original half-tone and line engravings. 1929. 8°. 271 pages. F. A. Davis Company, Philadelphia. $2.50.

A Practical Treatise on Disorders of the Sexual Function in the Male and Female. By Max Hühner, M.D. Third edition. 1929. 8°. 342 pages. F. A. Davis Company, Philadelphia. $3.00.

A System of Bacteriology in Relation to Medicine. By H. J. Bensted, W. Bulloch, L. Dudgeon, A. D. Gardner, and others. (Privy Council Medical Research Council) Volume 4. 1929. 8°. 482 pages. His Majesty's Stationery Office, London. $5.12.

Insects, Ticks, Mites, and Venomous Animals of Medical and Veterinary Importance. Part I, Medical. By Walter Scott Patton, M.B., Ch.B. (Edin.), F.E.S.

and ALWEN M. EVANS, D.Sc. Illustrated by Edith Mary Patton, Alwen M. Evans, and A. J. Engel Terzi. Photographs by M. Brown. With a Foreword by Emeritus Prof. Robert Newstead, F.R.S. 1929. 8°. 786 pages. H. R. Grubb, Ltd., Croydon. $5.00.

Diseases of the Blood. By PAUL W. CLOUGH, M.D. Harper's Medical Monographs. 1929. 16°. 310 pages. Harper and Brothers, Publishers, New York. $2.50.

Posture and Hygiene of the Feet. By PHILIP LEWIN, M.D. The National Health Series. Edited by the National Health Council. 1929. 24°. 47 pages. Funk and Wagnalls Company, New York. $0.35.

Epidemic Encephalitis. Etiology, Epidemiology, Treatment. Report of a Survey by the Matheson Commission. WILLIAM DARRACH, Chairman. 1929. 12°. 849 pages. Columbia University Press, New York.

Pettibone's Textbook of Physiological Chemistry With Experiments. By J. F. MCCLENDON, Ph.D. Revised and rewritten. Fourth edition. 1929. 8°. 368 pages. The C. V. Mosby Company, St. Louis. $3.75.

The Newer Knowledge of Nutrition. The Use of Foods for the Preservation of Vitality and Health. By E. V. MCCOLLUM, Ph.D., Sc.D. and NINA SIMMONDS, Sc. D. Illustrated. Fourth edition rewritten. 1929. 8°. 594 pages. The MacMillan Company, New York. $5.00.

The Science of Nutrition Simplified. By D. D. ROSEWARNE, M.R.C.S. (Eng.), L.R.C.P. (Lond.). Illustrated. 1929. 12°. 314 pages. The C. V. Mosby Company, St. Louis. $3.50.

Stone and Calculous Disease of the Urinary Organs. By J. SWIFT JOLY, M.D. (Dub.), F.R.C.S. (Eng.). With 189 illustrations in the text and four coloured plates. 1929. 8°. 568 pages. The C. V. Mosby Company, St. Louis. $16.00.

An Introduction to the Study of the Nervous System. By E. E. HEWER, D.Sc. (Lond.) and G. M. SANDES, M.B., B.S. (Lond.), M.R.C.S., L.R.C.P. 1929. 8°. 104 pages. The C. V. Mosby Company, St. Louis. $6.50.

A Frontier Doctor. By HENRY F. HOYT. With an Introduction By Frank B. Kellogg. And with Illustrations. 1929. 8°. 260 pages. Houghton Mifflin Company, Boston. $3.50.

The Internal Secretions of the Ovary. By A. S. PARKES, M.A. (Cantab.), Ph.D. (Manch.), D.Sc. (London). With illustrations. Monographs on Physiology. 1929. 8°. 242 pages. Longmans, Green and Company, New York. $7.50.

Hemorrhoids, the Injection Treatment and Pruritus Ani. By LAWRENCE GOLDBACHER, M.D. Illustrated with 31 half-tone and line engravings, some in colors. 1930. 8°. 205 pages. F. A. Davis Company, Philadelphia. $3.50.

Clinical Obstetrics. By PAUL T. HARPER, Ph.B., M.D., Sc.D., F.A.C.S. Illustrated with 84 plates of engravings (250 figures) with legends and charts. 1930. 8°. 629 pages. F. A. Davis Company, Philadelphia. $8.00.

The Volume of the Blood and Plasma. In Health and Disease. By LEONARD G. ROWNTREE, M.D., and GEORGE E. BROWN, M.D. With the Technical Assistance of Grace M. Roth. Illustrated. 1929. 12°. 219 pages. W. B. Saunders Company, Philadelphia. $3.00.

Oxford Medical Publications. Publisher: Humphrey Milford, London. The following four volumes.

Gastric and Duodenal Ulcer. By ARTHUR F. HURST, M.A., M.D. (Oxon.), F.R.C.P. and MATTHEW J. STEWART, M.B. (Glasg.), F.R.C.P. With the Co-Operation in the Radiological Sections of P. J. Briggs, M.A. (Cantab.), M.R.C.S., L.R.C.P. 1929. 8°. 544 pages. $20.00.

Common Infections of the Female Urethra and Cervix. By FRANK KIDD, M.A., M.Ch. (Cantab.), F.R.C.S. (England) and A. MALCOLM SIMPSON, B.A., M.B., D.P.H. (Cantab.). With additional chapters by George T. Western, M.D., and M. S. Mayou, F.R.C.S. 1929. 8°. 197 pages.

The Nervous Child. By HECTOR CHARLES CAMERON, M.A., M.D. (Cantab.) F.R.C.P. (Lond.). Fourth edition. 1929. 12°. 249 pages.

An Outline of Neurology and Its Outlook. By SIR E. FARQUHAR BUZZARD, K.C.V.O., M.A., M.D., F.R.C.P. Being the Eleventh Earl Grey Memorial Lecture Delivered at King's Hall Armstrong College, Newcastle-on-Tyne, March 11, 1929. 8°. 24 pages. $0.35.